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"Otolith and Vertical Canal Contributions to Dynamic Postural Control"

Summary: The objective of this project is to determine: 1) How do normal subjects adjust postural movements in response to changing or altered otolith input, for example, due to aging? and 2) How do patients adapt postural control after altered unilateral or bilateral vestibular sensory inputs such as ablative inner ear surgery or ototoxicity, respectively? The following hypotheses are under investigation: 1) Selective alteration of otolith input or abnormalities of otolith receptor function will result in distinctive spatial, frequency, and temporal patterns of head movements and body postural sway dynamics. 2) Subjects with reduced, altered, or absent vertical semicircular canal receptor sensitivity but normal otolith receptor function or *vice versa*, should show predictable alterations of body and head movement strategies essential for the control of postural sway and movement. The effect of altered postural movement control upon compensation and/or adaptation will be determined. These experiments provide data for the development of computational models of postural control in normals, vestibular deficient subjects and normal humans exposed to unusual force environments, including orbital space flight.

Key Words: Vestibular compensation, otolith, posture, posturography, human postural control, aging, ototoxicity, space flight, linear acceleration, microgravity.

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SPECIFIC AIMS & PROCEDURES

Project 1. Effect of Stable Unilateral & Bilateral Vestibular Abnormalities on Dynamic Postural Control.

Experiments were continued on subjects with well documented unilaterally or bilaterally abnormal vestibular function as demonstrated by a standard vestibuloocular (VOR) and/or vestibulospinal (VS) clinical test battery(1). Criteria for abnormality are vestibular function test values which lie outside 95% confidence intervals or $> \pm 2$ SD, depending upon the reference data base(2-5).

Subjects who met the screening criteria were recalled for centrifuge and modified dynamic posturography (DP) experiments. A modified NeuroCom[®] EquiTest[®] device was used for the DP testing. For the centrifuge experiments, constant velocity trapezoidal stimuli were used.

Abnormal subjects were screened and baselined for possible participation in additional studies. During all project years, more than 400 abnormal subjects were tested.

Initial results from one patient with small bilateral vestibular schwannomas (neurofibromatosis type 2, or NF2) have been reported before and after surgical removal(6). Results from this patient have very important theoretical implications because the inferior division of the vestibular nerve was preserved on one side and the superior division on the other. (Auditory function was preserved on both sides.) This was the first documented case in the human demonstrating the ability of the brain to integrate partial (both otolith and canal) vestibular spatial domains from the two ears for normal sensorimotor interactive control of pitch plane eye and body movement.

A project designed to determine the stoichometrics of visual-vestibular (VVOR) interactions has been completed. Results support the hypothesis that VVOR interactions are non-linear in normal subjects, but become linear under some conditions in abnormal subjects. For example, when VOR and OKN functions are normal, a non-linear "saturation constant"-- e.g. "unity gain" -- appears to govern VVOR interactions. However, when a critical gain threshold is reached in either the VOR or OKN system, interactions appear to become algebraic, but inadequate for compensation (unity gain). This non-linear dynamic appears to persist until all vestibular function is lost. VVOR interaction phase relationships are more complicated and will require further study. These findings were presented at the American Otologic Society meeting in Palm Desert, California, on April 30, 1995 and later published in the American Journal of Otology(7).

Nineteen healthy subjects and eight vestibular deficient (VD) subjects were exposed to an inter-aural centripetal acceleration. At intervals during the rotation they performed a series of head saccades toward randomly-presented visual targets. Eight of the

normal subjects also performed the same head-saccade protocol in a static-tilt chair adjusted to specific angles (providing a change in angle (direction) but not in magnitude of gravito-inertial force). Postural center-of-pressure (COP) measures and multisegment sway kinetics were also gathered before and within ten minutes after centrifugation. Normal subjects overestimated roll-tilt during centrifugation, and made errors in perception of head vertical as estimated by directed saccades. Postural COP, segmental body motion amplitude, and hip sway frequency increased significantly after centrifugation. Abnormal subjects under estimated roll-tilt during centrifugation and their directed saccades revealed permanent spatial distortions. Bilateral VD subjects subjects had poor baseline postural control and showed no further decrements after centrifugation. Unilateral VD subjects had varying degrees of postural decrements, both before and after centrifugation. These results suggest that orientation of the gravito-inertial vector and its magnitude are both used by the central nervous system for calibration of multiple orientation systems. A change in the gravito-inertial force (otolith input) can rapidly initiate postural and perceptual adaptation in several sensorimotor systems, independent of a structured visual surround. A manuscript is currently in revision(8).

Projects 2 and 3. Studies on young and elder normals.

In order to study longitudinal aging effects in postural control, peak to peak sway on 6 SOT conditions were measured in 36 normal subjects 10 years ago(4, 5) and again recently. (We have previously demonstrated that peak-to-peak sway is a robust measure of human upright control of posture after more than a decade of comparison of various signal processing techniques. This finding has been independently confirmed using both clinical and laboratory techniques(9). Postural control was well within normal range for all subjects when tested, i.e. none of the subjects were subclinically abnormal. (Normal data published in 1990(4) included subjects who satisfied study admission criteria but who clearly had subclinical abnormalities. The abnormal postural sway exhibited by vestibular deficient subjects has been reported(4, 10-12). Differences between the first and second tests were analyzed for changes (paired t test). There were no discernible differences for SOTs 1-4 (P>.15). Averages of SOT 5 and 6 peak-to-peak sway however were clearly larger 10 years after the first test. SOT 5 increased about 50% (t=4.86, 35 df, P=.000024) and SOT 6 increased over 50% (t=4.59, 35 df, P=.000055). Fifty percent changes as seen in SOT 5 and SOT 6 would be detectable with a power exceeding 90%.

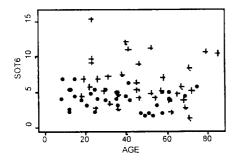


Figure 1: SOT 6 peak-to-peak sway as a function of age (first test, dark circles - second test 10 years later, plus signs). It is apparent that changes in SOT 6 are not due to a general age effect, since there is no age related trend.

The plot for SOT 5 against age has a similar appearance. The slopes of the linear regression of SOTs against age were not significantly different from zero. For SOT 6 (which showed the largest change), the maximum estimated decline of 0.51 in 10 years is small (about 33%) relative to the standard deviation.

Because the cross-sectional analysis published in 1990(4) indicated the presence of minima in some of the data sets, quadratic polynomials were fitted to the data. SOT 6 which previously seemed to have a pronounced minimum did not have statistically significant coefficients (F(2,69)=.54, P=.58).

The above findings are compatible with reports suggesting that the probability of disease (in this case, vestibular disorders) increases with age(13-16) and that balance may not worsen with age (<80years) per se unless there is concomitant or undiagnosed pathology. Our longitudinal study results support the latter conclusion, i.e. age per se is not associated with decline in postural control, at least until the age of 80 years. Recent results from the STS-95 study of a 77 year-old astronaut supports this conclusion(17). Quantitative analyses of a 77 year old astronaut's balance control performances revealed few differences between his neuro-adaptive responses to space flight and those from a younger group of astronauts, who ere tested following missions of similar duration. This suggests that the physiological changes associated with aging do not necessarily impair adaptive plasticity in the human following removal and subsequent reinsertion of gravity.

In addition, we have completed the baseline protocol on 6 elderly distinguished scientists in the fields of otology/audiology. This work has been done in conjunction with the "Old Time Ears" project (Principle Investigator Linda Hood, Ph.D.) Initial findings were presented as the Association for Research in Otolaryngology meeting in St. Petersberg, Florida, 1997. We are currently in the process of arranging for testing on the remaining 8 subjects (of 16 subjects in the "Old Time Ears" project, 6 have been tested, 2 (non-tested) have died, and 8 are yet to be tested.) Because of lack of funds, there has been no further progress on this study.

Project 4. Postural compensation/adaptation to abrupt changes in vestibular inputs.

During the first four years of this project, there were three main findings of interest to clinicians from the study of human postural control in astronauts: 1) the postural instability relative to preflight observed in all returning astronauts was demonstrated to be of vestibular origin, 2) previous experience ("efferent copy" or "re-afference") attenuates, but does not prevent postflight postural instability (at least for a total experience of three flights) and 3) visual inputs dominate during the early, rapid recovery and the somatosensory inputs dominate the later secondary phase of recovery. (Black, et al., Vestibular plasticity following orbital space flight: Recovery from postflight postural instability. Presented at the 18th Bárány Society Meeting, Uppsala, Sweden, 6-8 June, 1994)(18, 19).

During year four, we reported on the time constant of nystagmus slow phase velocity (SPV) to yaw-axis rotation as a function of the severity of unilateral canal paresis. We found that the time constant of the response both towards and away from the lesioned side decreased in proportion to increasing canal paresis; this supports the hypothesis that bilateral peripheral vestibular input is necessary for the mechanisms or processes underlying normal horizontal SPV storage(20).

As part of the Extended Duration Orbiter "Detailed Supplementary Objective 605" team, we completed the first large n study of balance control following spaceflight(21). We confirmed that postural ataxia following short duration spaceflight was vestibular in origin. Our results demonstrated that balance control is disrupted in all astronauts immediately after return from space, and concluded that otolith-mediated spatial reference provided by the terrestrial gravitational force vector is not used by the astronaut's balance systems immediately after spaceflight.

Our results demonstrate the positive adaptive control effect of prior space flight experience upon recovery of postural control after landing. The beneficial effect of previous experience upon improved performance immediately postflight has important implications for management of vestibular disorders on earth (including rehabilitation) and upon space flight countermeasure development.. This finding also suggests a reason for the variable results in vestibular physical therapy for peripheral vestibular disorders. Vestibular rehabilitation therapy (VRT) has proven to be one of the most effective management methods for some disorders such as benign paroxysmal positional nystagmus and vertigo, stable unilateral or incomplete bilateral vestibular loss. However if the disorder results from endolymphatic hydrops, including Meniere's disease which cause fluctuating vestibular function, VRT is usually not effective, depending upon status of residual vestibular function. That is, the hydrops must be controlled for optimal results from rehabilitation. The underlying principle appears to be the stability and normality of baseline vestibular function when the pathological process is superimposed and the status and stability of remaining vestibular function upon successful resolution of the pathology. Unpredictable changes in vestibular function invoke a search for an "efferent copy" or previous experience which may or may not exist in one's central nervous system. An efferent copy of a consistent change relative to baseline vestibular function is more likely to enable successful compensation strategies, allowing the brain to recognize the change and command appropriate neuromuscular responses(18, 22-24).

Adult subjects with the diagnosis of peripheral vestibular disorders were given a course of individualized vestibular rehabilitation therapy (VRT). Normal subjects and subjects with peripheral vestibular disorders who did *not* receive VRT served as controls. Results showed that an individualized program of VRT resulted in subjective and objective (documented by computerized dynamic posturography) improvement in all subjects with peripheral vestibular disorders, regardless of the diagnosis(25).

We have evaluated the recovery dynamics of ototoxicity in subjects who had received aminoglycosides(26). Partial or complete recovery of vestibular function occurred in 4 of 8 ototoxic subjects followed for one year, most of whom received gentamicin. There was no relation between cumulative gentamicin dose and ototoxicity. Of the most three severely affected subjects, two demonstrated complete or partial recovery of response HCVOR gain or time constant, relative to baseline. Dynamics of recovery were highly variable between individuals.

Six patients, 18-69 y/o, with unilateral vestibular loss were rotated in darkness on a fixed-chair centrifuge. Subjects were seated at 0.54 m from the center of rotation and were either 'facing the motion' or had their 'back to motion' for both clockwise and

counterclockwise rotations. Fixed radius angular velocity trapezoids (250 deg/s, acceleration/deceleration at 25 deg/s2) yielded a steady-state centrifugal force of 1.0g, which tilted the gravito-inertial force by 45deg. Somatosensory settings to perceived earth-horizontal were normal in 4 subjects and lower than normal in 2 subjects for some of the stimuli. This finding suggests that unilateral vestibular loss does not prevent normal perception of tilt during centrifugation. The effect of the centrifugal acceleration was estimated by subtracting horizontal eye movement responses (video-oculography recordings) during the 'back-to-motion' condition from the 'facing-motion' condition, for a same direction of rotation. When rotation occurs towards the healthy ear, the eye velocity resulting from this subtraction reaches 15 deg/s during the angular acceleration and then stabilizes around 1 deg/s. When rotation occurs towards the lesioned ear, there is no clear initial peak in eye velocity and the horizontal eye velocity remains around 2 deg/s during the whole duration of centrifugation. We conclude that the healthy ear produces a linear vestibulo-ocular reflex (VOR) for both direction of linear acceleration. During rotation towards the healthy ear, the combination of angular and linear VORs produces an eye movement response greater than the sum of each separate VOR. These results will be presented at the Ordinary Meeting of the Barany Society, Uppsala, Sweden, June, 2000. (Perceptual tilt and eye movement responses induced by centrifugation in patients with complete unilateral vestibular loss. Claire Gianna, F. Owen Black, and Daniel M. Merfeld.)

Technical Progress:

<u>Hydraulic Pitch Axis Rotation Device</u>. An existing hydraulic actuator has been modified for pitch and roll stimuli. The laboratory space for the device has been modified, a special wall mounted bracket supports the actuator and device frame, and the hydraulic lines and pump have been connected. Computer and safety control, and data analysis interfaces have been modified from existing software. All changes have been reviewed and approved by the Legacy IRB.

<u>Human-rated Centrifuge</u>. The human rated centrifuge has been completed and normal and abnormal subject experimental results have been summarized above.

<u>Video eye movement recording and analysis techniques.</u> An operational 3-D video eye movement and analysis system is in place in our laboratories. The binocular SMI VOG 3-D video eye movement recording and analysis system has been used successfully to conduct the above studies. We have reported our findings that noninvasive measurements of three-dimensional eye movements may be accurately achieved with video methods(27).

Modified dynamic posturography device. Progress has been made on the modification of the hydraulically powered computerized dynamic posturography device. The hydraulic system has been completely over-hauled. Software is being re-written for PC control and analysis (converted from DEC operating systems). In addition, the software is being "merged" with a "Flock-of-birds" multi-dimensional analysis system.

Budget.

The Final Financial Report (SF272) has been submitted and received by the Office of Naval Research, Seattle, WA.

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